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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/392,682	09/09/1999	DEITER C. GRUENERT	480.18-4	1612

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EXAMINER

KATCHEVES, KONSTANTINA T

ART UNIT	PAPER NUMBER
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1636

DATE MAILED: 06/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

09/392,682

Applicant(s)

GRUENERT ET AL.

Examiner

Konstantina Katcheves

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 29 September 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 17-35 and 37-44 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 17-35 and 37-44 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 09 September 1999 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_.
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_.

### **DETAILED ACTION**

Claims 17-35 and 37-44 are pending in the present application.

#### ***Continued Examination Under 37 CFR 1.114***

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 29 September 2003 has been entered.

#### ***Response to Amendment***

The art rejections of claims 17-35 and 37-44 are withdrawn in view of Applicant's amendment to the present claims.

The rejection under the doctrine of obviousness double patenting is maintained. Applicant's acknowledgement of the rejection and intent to file a terminal disclaimer upon indication of allowable subject matter is noted.

Claims 17-35 and 37-44 stand rejected under the enablement requirement of 35 U.S.C. 112, first paragraph, for the reasons already of record.

#### ***Response to Arguments***

Claims 17-35 and 37-44 stand rejected under the enablement requirement of 35 U.S.C. 112, first paragraph, for the reasons already of record.

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This rejection is maintained for the reasons of record found in each of the prior Office actions. For the purposes of compact prosecution, the arguments provided in those Office actions are not repeated herein; however, they remain applicable to these claims as amended. Applicant argues that the Declaration under 37 C.F.R. 1.132 by inventor, D. Dieter Gruenert, which teaches the SFHR-mediated modification of ion transport in nasal mucosa in a mouse model of cystic fibrosis establishes the present method works both *in vivo* and *ex vivo*. The declaration points to the disclosure of two exhibits in support of this position. These exhibits are discussed below.

The *ex vivo* results of the Prokopishyn et al. transcript (Exhibit A) method first fail to overcome the short coming of *in vivo* gene therapy methods. Second, regarding *ex vivo* methods the disclosure teaches that nude mouse models were used. Another factor in the efficacy of gene therapy methods is the immune system of the host organism. Whole animals have a sophisticated immune system that must be overcome for the effective *in vivo* transfection of cells whereas the mouse models often have compromised immune systems. The mouse models used by Prokopishyn et al. are immune compromised NOD/SCID mice wherein engraftment of transfected cells would face less difficulties presented by the host immune system. Even with these immunocompromized hosts the best data found in Prokopishyn et al. show 13 of 23 surviving mice with engrafted cell. This data, however, fails to lack of direction on how to ensure that cells from the *ex vivo* method would replace, or otherwise out-compete, the endogenous defective cells. Goncz et al. (Exhibit B) only teach the *in vitro* microinjection of isolated human hematopoietic stem/progenitor cells and site specific conversion of approximately 50% of these cells. The examiner does not dispute that the present method is

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enabled for *in vitro* practices. However, *in vitro* data does not overcome the weight of the evidence already of record that the present invention is not enabled for the full scope of the invention claimed.

Applicant also questions the legal basis of the present rejection. Applicant asserts that question of enablement for “the claimed method must be directed at the claimed method itself, and not at the shortcomings of the prior art.” Applicant is directed to disclosures in the art as evidence of the shortcomings of the present claims. The art provides evidence as to the state of the art, the relevant skill of those in the art, the quantity of experimentation necessary, and the predictability or unpredictability of the art, for example, each of these inquiries is relevant and necessary in determining whether the practice of the present method would require undue experimentation on the part of those of skill in the art. See *In re Wands*, 8 USPQ2d 1400, 1404 (CAFC 1988) (Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors to consider when assessing if a disclosure would have required undue experimentation).

Applicant argues that Exhibits C and Exhibits E, filed 3 December 2001, were not adequately addressed in the prior Office action. Applicant argues that “these *in vitro* studies augment the *in vitro* and *ex vivo* studies because they confirm that the method of replacement works in normal target cells as well as in transformed cells, and that reasonable inferences about functional correction can be drawn from structural evidence of target replacement.” As set forth in the prior Office actions, *in vivo* and *ex vivo* method are suspect for a number of reasons such as whether the *ex vivo* cell transplants would out compete or replace the endogenous defective cells or whether *in vivo* transfection methods would overcome the difficulties related to transfer

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such as the delivery vehicle, targeting of the appropriate cells and route of delivery. Applicant's own article Exhibit C, filed 3 December 2001, shows that those of the art are aware that *in vitro* work cannot be extrapolated to *in vivo* work. Applicant's own article, Exhibit C, states that "one difficulty in going from *in vitro* to *in vivo* experiments is that the conditions relevant to transfer (the delivery vehicle, the target and the route of delivery) are different. See Goncz, Exhibit C, filed 3 December 2001, pp.961-962 bridge.

Applicant also asserts that the *ex vivo* data of Exhibit G, file 3 December 2001, show that SHFR remained stable in human hematopoietic stem/progenitor cells for 5 weeks in up to 70% of the alleles *ex vivo*. First, for reasons similar to those discussed above, the *ex vivo* data fail to overcome the unpredictability of the art because they fail to show that the modification would be maintained *in vivo* because transplantation of the cells into an animal host is not shown.

Additionally, the *ex vivo* data do not show that the cells would be replace or out compete endogenous defective cells. Additionally, the disclosures of Exhibits C and F, filed 3 December 2001, were discussed by the Examiner and deemed not to fully enable the present invention.

Given that efficiency and sufficiency of delivery is one of the major obstacles to overcome in gene therapy, the delivery vehicle used is critical. None of the three delivery vehicles used in Exhibit C were taught or suggested in the instant specification. Thus, these articles do not serve to show the specification was enabled. The method of Exhibit F involve the *ex vivo* modification and subsequent transplantation method of isolated cells, which fails to fully enable the claims for the reasons discussed above. Moreover, the disclosure of Exhibit C, which is Applicant's own work, explicitly acknowledges the difficulty relevant to gene transfer and the importance of the

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delivery vehicle and the route of delivery in overcoming these difficulties. See Goncz, Exhibit C, filed 3 December 2001, pp.961-962 bridge.

### ***Conclusion***

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Konstantina Katcheves whose telephone number is (571) 272-0768. The examiner can normally be reached on Monday, Tuesday, Thursday and Friday 7:30 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel, Ph.D. can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

  
Konstantina Katcheves

Examiner  
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